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Dominique Michel

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EXAMINER

YOUNG, SHAWQUA

ART UNIT

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

DETAILED ACTION

Claims 1-8, 21-25 and 31-39 are currently pending in the instant application. Applicants have added new claims 37-39 in the amendment filed on May 18, 2009. Claims 1, 3-7, 21-24, 33 and 39 are rejected, claims 2, 8, 25, 31 and 32 are objected and claims 34, 36, 37 and 38 are allowed in this Office action.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 18, 2009 has been entered.

I. *Response to Arguments*

Applicant's arguments, filed May 18, 2009 has overcome the rejection of claims 2, 8, 25, 31, 32, 34 and 35 under 35 USC 103 as being unpatentable over Hill, et al in view of Matsumoto. The above rejection has been withdrawn relating to the indicated claims.

Applicant's arguments for the rejection of claims 1, 3-7, 21-24 and 33 have been considered but are not persuasive. Applicant argues that the Examiner has not

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properly shown in the record that the claimed invention is prima facie obvious.

Applicant argues that the differences between the instant claim 1 and the disclosure of Hill, et al. (even when Matsumoto is added) is inventive, patentable and unexpected over Hill, et al. Applicant further argues that the instant claim 1 primarily differs from Hill, et al. by working under pressure of at least 1.5 bar. Applicant states that applying pressure according to applicant's patentable process almost completely avoids formation of the tertiary amine and yields the secondary amine almost free of decomposition by-products regardless which residue R2 is attached to the amino source and that Hill, et al. is not even suggestive of this unexpected result. Applicant argues that the Examiner has not resolved the level of ordinary skill in the art and therefore there cannot be a valid rejection of obviousness under 103(a).

However, the Examiner disagrees with Applicant's arguments and maintains the position that the secondary reference shows the use of high pressure in the mannich reaction of ketones and secondary amines is considered to be a powerful method and gives good yields even with sterically demanding effects. Since the only "critical" difference between the prior art and the instant invention is the use of pressure in the first step of the reaction process, the secondary reference shows that the use of pressure was already present in a similar type of reaction and the general reaction claimed by Applicants has been taught in the primary reference (Hill). Therefore combining the two references shows that it would have been obvious for Applicants to perform the first step in the claimed invention under pressure because

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a) the art teaches the general reaction and b) the art teaches the use of high pressure for the Mannich reaction.

Applicant argues that the secondary reference is not even relevant to the primary reference because secondary amines are used in the Mannich reaction vs a primary amine used in the Hill, et al reference. The Examiner disagrees with Applicant's argument. The secondary reference shows that high pressure has been used in Mannich-type reactions which is what step(a) of Applicant's claimed invention is. The secondary reference shows that using high pressure is a "powerful method of aminomethylation and gives good yields". The use of high pressure in Mannich type reactions are known in the prior art. Applicants are modifying the reaction conditions of a known process (Hill, et al.) and according to In re Aller, modifying process conditions such as temperature and concentration is not a patentable modification absent a showing of criticality. The Examiner wants to point out that court rulings decided before Graham and KSR still are effective. Applicant has failed to point out where in the Graham decision or the KSR decision, it states that decisions such as In re Aller are no longer effective. The Examiner also wants to point out that Applicant has failed to provide the unexpected results discussed in the arguments in a declaration. Therefore, the Examiner has maintained the rejection of claims 1, 3-7, 21-24, 33 and 39 under 35 USC 103 rejection as being unpatentable over Hill, et al. in view of Matsumoto.

II. ***Rejection(s)***

35 USC § 103 - OBVIOUSNESS REJECTION

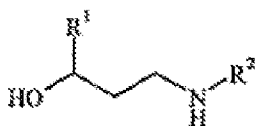
The following is a quotation of 35 U.S.C. § 103(a) that forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Graham v. John Deere Co. set forth the factual inquiries necessary to determine obviousness under 35 U.S.C. § 103(a). See *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). Specifically, the analysis must employ the following factual inquiries:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

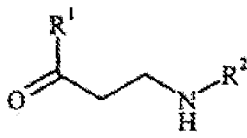
Claims 1, 3-7, 21-24, 33, 35 and 39 are rejected under 35 U.S.C. § 103(a) as being unpatentable over *Hill, et al.* in view of Matsumoto. Applicants claim The instant invention claims a process for the preparation of a compound of formula



and/or an addition salt of a proton acid, wherein R¹ represents C₁₋₈-alkyl or phenyl and R² represents alkyl, cycloalkyl, aryl or aralkyl, each aryl or aralkyl being optionally further substituted with alkyl, alkoxy and/or halogen which process comprises the following steps: a) reacting a mixture comprising: (i) a methyl ketone of

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formula: CH_3COR^1 wherein R^1 is as defined above, and (ii) a compound of formula: $\text{H}_2\text{N-R}^2$ and/or an addition salt of proton acid, wherein R^2 is as defined above, and (iii) formaldehyde or a source of formaldehyde selected from the group consisting of formaldehyde in aqueous solution, 1,3,5-trioxane, paraformaldehyde and mixtures thereof, in the presence of a solvent selected from the group consisting of water, aliphatic alcohols, cycloaliphatic alcohols and mixtures thereof and optionally a proton

acid to provide a β -keto amine of the formula  and/or an addition salt of a proton acid and b) reducing the carbonyl group of β -keto amine to afford a compound of formula I and/or an addition salt of a proton acid wherein the step a) is carried out at a pressure above 1.5 bar.

The Scope and Content of the Prior Art (MPEP §2141.01)

Hill, et al. teaches the following method



wherein a) $(\text{HCHO})_n$, MeNH_2

HCl , EtOH , HCl , reflux; b) H_2O , steam distillation, MeOH ; c) NaBH_4 , 2-propanol/ H_2O ;

d) MeOH , HCl ; $\text{EtOH}/\text{Me}_2\text{CO}$; R is H or Cl .

The secondary reference, *Matsumoto*, teaches the use of high pressure in the Mannich reaction of ketones and esters with dichloromethane and secondary amines.

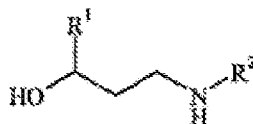
The secondary references teaches various reactions such as reacting $\text{PhCOCH}_2\text{CH}_3$ with $(\text{Et})_2\text{NH}$ under high pressure.

The Difference Between the Prior Art and the Claims (MPEP §2141.02)

The difference between the prior art of *Hill, et al.* and the instant invention is that there is that step a) in the instant application is carried out at a pressure above 1.5 whereas in the prior art primary reference the first step is carried out under reflux and then steam distillation.

Prima Facie Obviousness-The Rational and Motivation (MPEP §2142-2413)

In *In re Aller*, 220 F.2d 454, 105 USPQ 233 (CCPA 1955), it was well established that merely modifying the process conditions such as temperature and concentration is not a patentable modification absent a showing of criticality. For example, it is obvious



to modify the preparation of a compound of comprising step a) and step b) as disclosed in claim 1 to improve the product yield since a similar reaction using different conditions in step 1 was already taught by the primary reference and the use of high pressure in the Mannich reaction was taught by the secondary reference. Specifically, changing the reaction conditions of step 1 as seen in the claim 1 absent unexpected results is deemed obvious over the *Hill, et al.* reference in view of the secondary reference Matsumoto. The motivation for one of ordinary skill in the art to modify the first step of the prior art's reaction by using high pressure would be to develop a more efficient method for preparing amino alcohols. Therefore, it would have

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been prima facie obvious to one having ordinary skill in the art at the time the invention was made to attempt to improve the known process by modifying the reaction conditions (i.e. carrying out the first step under pressure) to increase the product yield when the secondary reference teaches the Mannich reaction of ketones and esters with dichloromethane and secondary amines under high pressure. A strong prima facie obviousness has been established.

III. *Objection(s)*

Dependent Claim Objections

Dependent Claims 2, 8, 25, 31 and 32 are also objected to as being dependent upon a rejected based claim. To overcome this objection, Applicant should rewrite said claims in an independent form and include the limitations of the base claim and any intervening claim.

IV. *Conclusion*

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shawquia Young whose telephone number is 571-272-9043. The examiner can normally be reached on 7:00 AM-3:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on 571-272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Shawquia Young/

Examiner, Art Unit 1626

/Rebecca L Anderson/

Primary Examiner, Art Unit 1626